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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,629	07/01/2003	Baochuan Guo	27433/04012	1402
24024	7590	11/14/2006	EXAMINER	
CALFEE HALTER & GRISWOLD, LLP 800 SUPERIOR AVENUE SUITE 1400 CLEVELAND, OH 44114				BERTAGNA, ANGELA MARIE
		ART UNIT		PAPER NUMBER
		1637		

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/611,629	GUO, BAOCHUAN
	Examiner	Art Unit
	Angela Bertagna	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 01 September 2006.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-13 and 15-30 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-13 and 15-30 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

FINAL REJECTION

Status of the Application

1. Applicant's response filed September 1, 2006 is acknowledged. Claims 1-13 and 15-30 are currently pending. Claims 1, 3, 4, 17-19, 25, and 27 were amended and claim 14 was cancelled in the response. Claims 28-30 are new.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Provisional Application No. 60/392,251, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. With regard to claim 21, the detection of mutant NR-21 microsatellites is not disclosed. Accordingly, claim 21 has not been granted benefit of the earlier filing date, and the original filing date, July 1, 2003, has been used for prior art purposes.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1, 2, 5-9, 11, 12, 15, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Afonina et al. (PNAS (1996) 93: 3199-3204; newly cited) in view of Sun et al. (Nature Biotechnology (February 2002) 19: 186-189).

Afonina teaches a method of specifically arresting primer extension on a single-stranded DNA target using a blocking oligonucleotide conjugated to a minor groove binder (see abstract).

Regarding claim 1, Afonina teaches a method comprising:

- a) selecting an extension primer complementary to a first target sequence in a single-stranded wild-type polynucleotide (page 3200, column 2, "Primer extension" section)
- b) selecting a probe complementary to a second target sequence in the wild-type polynucleotides, wherein the second target sequence is located 3' of the first target sequence on the wild-type polynucleotide strand (page 3200, column 2, "Primer extension" section)
- c) simultaneously contacting the polynucleotides in the mixture with the extension primer and the probe under conditions where the probe preferentially anneals to the second target sequence on the wild-type polynucleotide (page 3200, column 2 – page 3201, column 1, "Primer extension" section)

d) contacting the polynucleotides in the mixture with a DNA polymerase and nucleoside triphosphates under conditions where the extension primer is extended by polynucleotide synthesis, using the wild-type polynucleotide as a template, to produce extension products, wherein polynucleotide synthesis that uses the wild-type polynucleotides as templates is blocked by the probe (pages 3200-3201, “Primer extension” section; see also Figure 2 and pages 3201-3202, “Primer extension” section).

Regarding claim 6, Afonina teaches that like the minor groove binder-modified probe, peptide nucleic acid probes also form stable hybrids that may result in blocking primer extension (page 3199).

Regarding claim 7, the probe taught by Afonina is an oligonucleotide (see page 3200 and Table 1).

Regarding claim 8, Afonina teaches the use of blocking oligonucleotides with a phosphorothioated backbone (page 3201, column 2).

Regarding claim 9, Afonina teaches that the 3' end of the oligonucleotide is modified such that it cannot be extended (page 3202, column 1, where the 3' end was capped).

Regarding claim 11, Afonina teaches that the probe is a modified oligonucleotide (see abstract and pages 3200-3201).

Regarding claim 12, Afonina teaches that the extension primer and blocking probe hybridize to the wild-type template with different Tms, with the Tm of the blocking probe being higher than the Tm for the extension primer (see Table 1, where several of the blocking oligonucleotides have a Tm greater than the Tm of the primer (approximately 50C)).

Regarding claim 25, Afonina teaches a method comprising:

- a) contacting a single-stranded wild-type polynucleotide with a probe complementary to a second target sequence located 3' of a first target sequence in the same strand of the wild-type polynucleotide (pages 3200-3201, "Primer extension" section)
- b) simultaneously with step (a) above, contacting the single-stranded wild-type polynucleotide template with an extension primer complementary to the first target sequence in the wild-type polynucleotide to anneal the primer to the first target sequence (pages 3200-3201, "Primer extension" section)
- c) contacting the mixture with a DNA polymerase and nucleoside triphosphates to extend the extension primers annealed to the polynucleotides by polynucleotide synthesis (pages 3200-3201, "Primer extension" section), wherein polynucleotide synthesis of the wild-type polynucleotide is blocked by the hybridized probe (pages 3201-3202, "Primer extension" section; see also Figure 2).

Afonina tested the ability of several mismatched oligonucleotides to block primer extension, but only conducted the primer extension reaction using a wild-type template rather than a mixture of wild-type and mutant nucleic acids. Also, Afonina teaches simultaneous addition of the extension primer and blocking probe rather than the claimed sequential addition.

Sun teaches a PCR-based method of detecting mutant sequences in a mixture of wild-type and mutant nucleic acids. In the method taught by Sun, amplification of the wild-type sequence is blocked by addition of a blocking probe complementary to a sequence found in the

wild-type polynucleotide, but not in the mutant polynucleotide (see abstract for a general description).

Regarding claim 1, Sun teaches a method for detecting a mutant polynucleotide in a mixture of mutant and wild-type polynucleotides, comprising:

a) selecting an extension primer complementary to a first target sequence in the mutant and wild-type polynucleotides (Experimental protocol, page 188, where in the second round of PCR primers to the constant region are complementary to both wild-type and mutant polynucleotides)

b) selecting a probe complementary to a second target sequence in the wild-type polynucleotides but not in the mutant polynucleotides, wherein the second target sequence is located 3' of the first target sequence in the wild-type polynucleotide strand (Experimental protocol, page 188, where the PNA probe hybridizes to the wild-type but not the mutant sequence)

c) contacting the polynucleotides in the mixture with the probe under conditions where the probe preferentially anneals to the second target sequence but does not anneal to the mutant polynucleotides (Experimental protocol, pages 188-189, specifically the second round of PCR where the PNA probe is included)

d) simultaneously with step (c) above, contacting the polynucleotides in the mixture with the extension primer under conditions where the primer anneals to the first target sequence (Experimental protocol, pages 188-189, specifically the second round of PCR where the PNA probe is included with primers complementary to the constant region)

e) contacting the polynucleotides in the mixture with a DNA polymerase and nucleoside triphosphates under conditions where the extension primers are extended by polynucleotide synthesis, using the mutant and wild-type polynucleotides as templates, to produce extension products, wherein polynucleotide synthesis that uses the wild-type polynucleotides as templates is blocked by the probe (Experimental protocol, pages 188-189)

f) detecting the presence of mutant polynucleotide extension products (page 189, where the mutant extension products are detected by MALDI-TOF).

Regarding claim 2, Sun teaches that the mutant polynucleotides contain substitution mutations, as compared to the wild-type polynucleotides (page 187, column 1, first paragraph).

Regarding claim 5, Sun teaches that the extension primer has one or more attached biotin molecules (page 189 where the K-ras primer is biotinylated at the 5'end).

Regarding claim 6, Sun teaches that the probe is a peptide nucleic acid (Experimental protocol, page 188).

Regarding claim 15, Sun teaches that the extension products are isolated from the mixture by a solid phase extraction method (page 189, where isolation using chromatographic ZipTips is a solid phase extraction method).

Regarding claim 25, Sun teaches a method for selectively amplifying a mutant polynucleotide, in a mixture comprising mutant and wild-type polynucleotides, both the mutant polynucleotide and the wild-type polynucleotides having the same first target sequence, the wild-type polynucleotide having a second target sequence not present in the mutant polynucleotide, at least part of the second target sequence being located 3' of the first target sequence on the same polynucleotide strand of the wild-type polynucleotide, comprising:

a) contacting the mixture with a probe complementary to the second target sequence to preferentially anneal the probe to the second target sequence of the wild-type polynucleotide rather than to a corresponding sequence in the mutant polynucleotide (Experimental protocol, pages 188-189, where the PNA probe hybridizes to the wild-type but not the mutant sequence)

b) simultaneously with step (a) above, contacting the mixture with an extension primer complementary to the first target sequence in both the mutant and wild-type polynucleotides to anneal the primer to the first target sequence in both polynucleotides (Experimental protocol, page 188, where in the second round of PCR primers to the constant region are complementary to both wild-type and mutant polynucleotides)

c) contacting the mixture with a DNA polymerase and nucleoside triphosphates to extend the extension primers annealed to the polynucleotides by polynucleotide synthesis, the probe annealed to the wild-type polynucleotide limiting polynucleotide synthesis of the extension primer annealed to the wild-type polynucleotide, wherein the polynucleotide synthesis that uses the wild-type polynucleotide is blocked by the probe and the polynucleotide synthesis that uses the mutant polynucleotide is not blocked (Experimental protocol, pages 188-189).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the method of Afonina to the detection of mutant polynucleotides. Afonina taught that primer extension on a single-stranded template was specifically blocked by a complementary oligonucleotide conjugated to a minor groove binder annealed to the template downstream of the extension primer (pages 3201-3202 cited above). Afonina noted that only blocking oligonucleotides that were perfectly complementary to the template strand were capable

of completely blocking primer extension (page 3201, column 2 – page 3202, column 1), thereby suggesting to an ordinary practitioner that the extension of a mutant polynucleotide would not be blocked by a probe perfectly complementary to a sequence found only in the wild-type polynucleotide. Afonina also stated, “The hybridization properties of ODN-CPDI3 conjugates warrant their further evaluation as diagnostic probes and as potential PCR clamping agents (page 3203, column 2).” Since Sun taught that PCR clamping was a highly “sensitive, specific, and robust method for detecting mutations (pages 187-188)”, an ordinary practitioner would have been motivated to perform the method taught by Afonina using a mixture of mutant and wild-type polynucleotides in order to extend the applicability of the method to mutation detection. Since Afonina expressly suggested using the oligonucleotides in PCR clamping reactions (page 3203, column 2), an ordinary practitioner would have been motivated to use the minor groove binder-conjugated oligonucleotides in either a PCR format as taught by Sun or the primer extension format taught by Afonina to detect mutant sequences in a mixture of wild-type and mutant polynucleotides. Finally, although neither Afonina nor Sun teach sequential addition of the primer and probe, MPEP 2144.04 IV.C notes, “Selection of any order of mixing ingredients is *prima facie* obvious.” Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the probe first followed by the primer. Afonina even stated, “Inhibition of primer extension did not require a preannealing step (page 3202, column 2).” Therefore, in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is *prima facie* obvious as noted by the MPEP section above. The combined teachings of Afonina and Sun result in the instant claims 1, 2, 5-9, 11, 12, 15, and 25.

5. Claims 1, 2, 6-12, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Afonina et al. (PNAS (1996) 93: 3199-3204; newly cited) in view of Rampersad et al. (US 5,830,712).

Afonina teaches a method of specifically arresting primer extension on a single-stranded DNA target using a blocking oligonucleotide conjugated to a minor groove binder (see abstract).

Regarding claim 1, Afonina teaches a method comprising:

- a) selecting an extension primer complementary to a first target sequence in a single-stranded wild-type polynucleotide (page 3200, column 2, “Primer extension” section)
- b) selecting a probe complementary to a second target sequence in the wild-type polynucleotides, wherein the second target sequence is located 3' of the first target sequence on the wild-type polynucleotide strand (page 3200, column 2, “Primer extension” section)
- c) simultaneously contacting the polynucleotides in the mixture with the extension primer and the probe under conditions where the probe preferentially anneals to the second target sequence on the wild-type polynucleotide (page 3200, column 2 – page 3201, column 1, “Primer extension” section)
- d) contacting the polynucleotides in the mixture with a DNA polymerase and nucleoside triphosphates under conditions where the extension primer is extended by polynucleotide synthesis, using the wild-type polynucleotide as a template, to produce extension products, wherein polynucleotide synthesis that uses the wild-type polynucleotides as templates is blocked by the probe (pages 3200-3201, “Primer extension” section; see also Figure 2 and pages 3201-3202, “Primer extension” section).

Regarding claim 6, Afonina teaches that like the minor groove binder-modified probe, peptide nucleic acid probes also form stable hybrids that may result in blocking primer extension (page 3199).

Regarding claim 7, the probe taught by Afonina is an oligonucleotide (see page 3200 and Table 1).

Regarding claim 8, Afonina teaches the use of blocking oligonucleotides with a phosphorothioated backbone (page 3201, column 2).

Regarding claim 9, Afonina teaches that the 3' end of the oligonucleotide is modified such that it cannot be extended (page 3202, column 1, where the 3' end was capped).

Regarding claim 11, Afonina teaches that the probe is a modified oligonucleotide (see abstract and pages 3200-3201).

Regarding claim 12, Afonina teaches that the extension primer and blocking probe hybridize to the wild-type template with different Tms, with the Tm of the blocking probe being higher than the Tm for the extension primer (see Table 1, where several of the blocking oligonucleotides have a Tm greater than the Tm of the primer (approximately 50C)).

Regarding claim 25, Afonina teaches a method comprising:

- a) contacting a single-stranded wild-type polynucleotide with a probe complementary to a second target sequence located 3' of a first target sequence in the same strand of the wild-type polynucleotide (pages 3200-3201, "Primer extension" section)
- b) simultaneously with step (a) above, contacting the single-stranded wild-type polynucleotide template with an extension primer complementary to the first target sequence in

the wild-type polynucleotide to anneal the primer to the first target sequence (pages 3200-3201, “Primer extension” section)

c) contacting the mixture with a DNA polymerase and nucleoside triphosphates to extend the extension primers annealed to the polynucleotides by polynucleotide synthesis (pages 3200-3201, “Primer extension” section), wherein polynucleotide synthesis of the wild-type polynucleotide is blocked by the hybridized probe (pages 3201-3202, “Primer extension” section; see also Figure 2).

Afonina tested the ability of several mismatched oligonucleotides to block primer extension, but only conducted the primer extension reaction using a wild-type template rather than a mixture of wild-type and mutant nucleic acids. Also, Afonina teaches simultaneous addition of the extension primer and blocking probe rather than the claimed sequential addition.

Rampersad teaches a method of blocking extension of wild-type polynucleotides in a mixture of wild-type and mutant nucleic acids (see abstract).

Regarding claim 1, Rampersad teaches a method for detecting a mutant polynucleotide in a mixture of mutant and wild-type polynucleotides, comprising:

a) selecting an extension primer complementary to a first target sequence in the mutant and wild-type polynucleotides (Example 2, column 6, lines 25-30, where the degenerate oligonucleotides are complementary to wild-type and mutant polynucleotides. Since Rampersad stated that the claimed method is designed to inactivate undesirable members, where undesirable members are defined as those members of the sample that interfere with the use of the sample.

Therefore disclosure of Rampersad encompasses undesirable members that are wild-type or mutant polynucleotides)

- b) selecting a probe complementary to a second target sequence in the wild-type polynucleotides but not in the mutant polynucleotides, wherein the second target sequence is located 3' of the first target sequence in the wild-type polynucleotide strand (Example 2, column 6, lines 33-40, where the "blockers" satisfy these limitations)
- c) contacting the polynucleotides in the mixture with the probe under conditions where the probe preferentially anneals to the second target sequence but does not anneal to the mutant polynucleotides (Example 2, column 6, lines 41-45)
- d) simultaneously with step (c) above, contacting the polynucleotides in the mixture with the extension primer under conditions where the primer anneals to the first target sequence (Example 2, column 6, lines 41-45)
- e) contacting the polynucleotides in the mixture with a DNA polymerase and nucleoside triphosphates under conditions where the extension primers are extended by polynucleotide synthesis, using the mutant and wild-type polynucleotides as templates, to produce extension products, wherein polynucleotide synthesis that uses the wild-type polynucleotides as templates is blocked by the probe (Example 2, column 6, lines 41-67)
- f) detecting the presence of mutant polynucleotide extension products (Example 2, column 6, lines 41-67).

Regarding claim 2, Rampersad teaches that the mutant polynucleotides contain deletion mutations, insertion mutations, substitution mutations or a combination of deletion, insertion and substitution mutations, as compared to the wild-type polynucleotides (see abstract and column 2,

lines 44-50 where the nucleic acid family inherently includes deletions, insertions, substitutions, and combinations thereof).

Regarding claim 7, Rampersad teaches that the probe is an oligonucleotide (Example 2, column 6, lines 33-37).

Regarding claim 8, Rampersad teaches that at least part of the oligonucleotide has a phosphorothioated backbone (column 3, lines 65-67).

Regarding claim 9, Rampersad teaches that the oligonucleotide has a 5' end and a 3' end and the 3' end is modified such that it cannot be extended by polynucleotide synthesis (column 3, lines 52-53).

Regarding claim 10, Rampersad teaches that the nucleotide at the 3' end of the oligonucleotide is phosphorylated (column 3, lines 63-64).

Regarding claim 11, Rampersad teaches that the probe is a modified oligonucleotide (column 3, lines 63-67; where the addition of an amine, phosphate, acridine or cholesterol group to the probe results in a modified oligonucleotide).

Regarding claim 12, Rampersad teaches that:

- a) there is a first T_m for annealing of the extension primer to the first target sequence (column 6, lines 46-53, where the first T_m is 52°C)
- b) there is a second T_m for annealing of the probe to the second target sequence (column 6, lines 46-53, where the second T_m is 65°C)
- c) there is a third T_m for annealing of the probe to the mutant polynucleotides, wherein the second T_m is higher than the first T_m ; and wherein the first T_m is higher than the third T_m (see Example 2, lines 46-67, note that T_{m2} (65°C) > T_{m1} (52°C)).

With regard to step (c) above, although Rampersad does not specifically disclose the presence of a third T_m that is lower than the first T_m , this is inherent. Rampersad explicitly discussed the importance of conducting the PCR under conditions where the blocker oligonucleotide can only hybridize to the undesirable sequences, and particularly pointed out that the T_m of the blocker oligonucleotide must be higher than the T_m of the primers (column 6, lines 49-61). Furthermore, for the method of Rampersad to function properly, the T_m for probe hybridization to the undesirable sequences (analogous to the instant wild-type sequences), must be lower than the T_m for primer annealing. Otherwise, the probe would hybridize to the desirable and undesirable sequences, thereby preventing preferential amplification of the desirable sequences, which is the object of the method of Rampersad. Therefore, the method of Rampersad must include a third T_m , for hybridization of the blocker oligonucleotide to the mutant (desirable) sequences, and this T_m must be lower than the T_m for primer annealing. Therefore, the disclosure of Rampersad meets the instant limitations.

Regarding claim 25, Rampersad teaches a method for selectively amplifying a mutant polynucleotide, in a mixture comprising mutant and wild-type polynucleotides, both the mutant polynucleotide and the wild-type polynucleotides having the same first target sequence, the wild-type polynucleotide having a second target sequence not present in the mutant polynucleotide, at least part of the second target sequence being located 3' of the first target sequence on the same polynucleotide strand of the wild-type polynucleotide, comprising:

- a) contacting the mixture with a probe complementary to the second target sequence to preferentially anneal the probe to the second target sequence of the wild-type polynucleotide

rather than to a corresponding sequence in the mutant polynucleotide (Example 2, column 6, lines 33-45, where the “blockers” satisfy these limitations)

b) simultaneously with step (a) above, contacting the mixture with an extension primer complementary to the first target sequence in both the mutant and wild-type polynucleotides to anneal the primer to the first target sequence in both polynucleotides (Example 2, column 6, lines 25-30 and 41-45, where the degenerate oligonucleotides are complementary to wild-type and mutant polynucleotides)

c) contacting the mixture with a DNA polymerase and nucleoside triphosphates to extend the extension primers annealed to the polynucleotides by polynucleotide synthesis, the probe annealed to the wild-type polynucleotide limiting polynucleotide synthesis of the extension primer annealed to the wild-type polynucleotide, wherein the polynucleotide synthesis that uses the wild-type polynucleotide is blocked by the probe and the polynucleotide synthesis that uses the mutant polynucleotide is not blocked (Example 2, column 6, lines 41-67).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the method of Afonina to the detection of mutant polynucleotides. Afonina taught that primer extension on a single-stranded template was specifically blocked by a complementary oligonucleotide conjugated to a minor groove binder annealed to the template downstream of the extension primer (pages 3201-3202 cited above). Afonina noted that only blocking oligonucleotides that were perfectly complementary to the template strand were capable of completely blocking primer extension (page 3201, column 2 – page 3202, column 1), thereby suggesting to an ordinary practitioner that the extension of a mutant polynucleotide would not be

blocked by a probe perfectly complementary to a sequence found only in the wild-type polynucleotide. Afonina also stated, "The hybridization properties of ODN-CPDI3 conjugates warrant their further evaluation as diagnostic probes and as potential PCR clamping agents (page 3203, column 2)." Since Rampersad taught that the above PCR blocking was an advantageous method of eliminating amplification of undesirable nucleic acid sequences (see abstract), an ordinary practitioner would have been motivated to perform the method taught by Afonina using a mixture of mutant and wild-type polynucleotides in order to extend the applicability of the method to mutation detection. Since Afonina expressly suggested using the oligonucleotides in PCR clamping (i.e. blocking) reactions (page 3203, column 2), an ordinary practitioner would have been motivated to use the minor groove binder-conjugated oligonucleotides in either a PCR format as taught by Rampersad or the primer extension format taught by Afonina to detect mutant sequences in a mixture of wild-type and mutant polynucleotides. Finally, although neither Afonina nor Rampersad teach sequential addition of the primer and probe, MPEP 2144.04 IV.C notes, "Selection of any order of mixing ingredients is *prima facie* obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the probe first followed by the primer. Afonina even stated, "Inhibition of primer extension did not require a preannealing step (page 3202, column 2)." Therefore, in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is *prima facie* obvious as noted by the MPEP section above. The combined teachings of Afonina and Rampersad result in the instant claims 1, 2, 6-12, and 25.

6. Claims 1-3, 6-9, 11-13, 25, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Afonina et al. (PNAS (1996) 93: 3199-3204; newly cited) in view of Orum et al. (Nucleic Acids Research (1993) 21(23): 5332-5336).

Afonina teaches a method of specifically arresting primer extension on a single-stranded DNA target using a blocking oligonucleotide conjugated to a minor groove binder (see abstract).

Regarding claim 1, Afonina teaches a method comprising:

- a) selecting an extension primer complementary to a first target sequence in a single-stranded wild-type polynucleotide (page 3200, column 2, “Primer extension” section)
- b) selecting a probe complementary to a second target sequence in the wild-type polynucleotides, wherein the second target sequence is located 3' of the first target sequence on the wild-type polynucleotide strand (page 3200, column 2, “Primer extension” section)
- c) simultaneously contacting the polynucleotides in the mixture with the extension primer and the probe under conditions where the probe preferentially anneals to the second target sequence on the wild-type polynucleotide (page 3200, column 2 – page 3201, column 1, “Primer extension” section)
- d) contacting the polynucleotides in the mixture with a DNA polymerase and nucleoside triphosphates under conditions where the extension primer is extended by polynucleotide synthesis, using the wild-type polynucleotide as a template, to produce extension products, wherein polynucleotide synthesis that uses the wild-type polynucleotides as templates is blocked by the probe (pages 3200-3201, “Primer extension” section; see also Figure 2 and pages 3201-3202, “Primer extension” section).

Regarding claim 6, Afonina teaches that like the minor groove binder-modified probe, peptide nucleic acid probes also form stable hybrids that may result in blocking primer extension (page 3199).

Regarding claim 7, the probe taught by Afonina is an oligonucleotide (see page 3200 and Table 1).

Regarding claim 8, Afonina teaches the use of blocking oligonucleotides with a phosphorothioated backbone (page 3201, column 2).

Regarding claim 9, Afonina teaches that the 3' end of the oligonucleotide is modified such that it cannot be extended (page 3202, column 1, where the 3' end was capped).

Regarding claim 11, Afonina teaches that the probe is a modified oligonucleotide (see abstract and pages 3200-3201).

Regarding claim 12, Afonina teaches that the extension primer and blocking probe hybridize to the wild-type template with different Tms, with the Tm of the blocking probe being higher than the Tm for the extension primer (see Table 1, where several of the blocking oligonucleotides have a Tm greater than the Tm of the primer (approximately 50C)).

Regarding claim 25, Afonina teaches a method comprising:

a) contacting a single-stranded wild-type polynucleotide with a probe complementary to a second target sequence located 3' of a first target sequence in the same strand of the wild-type polynucleotide (pages 3200-3201, "Primer extension" section)

b) simultaneously with step (a) above, contacting the single-stranded wild-type polynucleotide template with an extension primer complementary to the first target sequence in

the wild-type polynucleotide to anneal the primer to the first target sequence (pages 3200-3201, “Primer extension” section)

c) contacting the mixture with a DNA polymerase and nucleoside triphosphates to extend the extension primers annealed to the polynucleotides by polynucleotide synthesis (pages 3200-3201, “Primer extension” section), wherein polynucleotide synthesis of the wild-type polynucleotide is blocked by the hybridized probe (pages 3201-3202, “Primer extension” section; see also Figure 2).

Afonina tested the ability of several mismatched oligonucleotides to block primer extension, but only conducted the primer extension reaction using a wild-type template rather than a mixture of wild-type and mutant nucleic acids. Also, Afonina teaches simultaneous addition of the extension primer and blocking probe rather than the claimed sequential addition.

Orum teaches a method for detecting mutant polynucleotides comprising PCR clamping using a PNA blocking probe (see abstract).

Regarding claim 1, Orum teaches a method for detecting a mutant polynucleotide in a mixture of mutant and wild-type polynucleotides, comprising:

- a) selecting an extension primer complementary to a first target sequence in the mutant and wild-type polynucleotides (page 5335, Figure 6, where the common reverse primer is complementary to both the wild-type and mutant polynucleotides)
- b) selecting a probe complementary to a second target sequence in the wild-type polynucleotides but not in the mutant polynucleotides, wherein the second target sequence is

located 3' of the first target sequence in the wild-type polynucleotide strand (page 5335, Figure 6, where the PNA62 probe hybridizes to the wild-type, but not the mutant plasmid)

- c) contacting the polynucleotides in the mixture with the probe under conditions where the probe preferentially anneals to the second target sequence but does not anneal to the mutant polynucleotides (page 5335, Figure 6)
- d) simultaneously with step (c) above, contacting the polynucleotides in the mixture with the extension primer under conditions where the primer anneals to the first target sequence (page 5335, Figure 6)
- e) contacting the polynucleotides in the mixture with a DNA polymerase and nucleoside triphosphates under conditions where the extension primers are extended by polynucleotide synthesis, using the mutant and wild-type polynucleotides as templates, to produce extension products, wherein polynucleotide synthesis that uses the wild-type polynucleotides as templates is blocked by the probe (page 5335, Figure 6)
- f) detecting the presence of mutant polynucleotide extension products (Figure 6, page 5335, where the products are detected by agarose gel electrophoresis).

Regarding claim 2, Orum teaches that the mutant polynucleotides contain deletion mutations, insertion mutations, substitution mutations or a combination of deletion, insertion and substitution mutations, as compared to the wild-type polynucleotides (Figure 6, page 5335, where the mutant plasmids contain point substitutions).

Regarding claim 3, Orum teaches that the mutant and wild-type polynucleotides are isolated from the mixture of mutant polynucleotides, wild-type polynucleotides and unrelated polynucleotides before the step of contacting the polynucleotides with the probe (Methods

section, page 5333, first and third paragraphs, where the wild-type and mutant plasmids were separately isolated from a mini-library and then added to the PCR mixture at concentrations of 0.1 ng per plasmid, thereby eliminating the presence of unrelated polynucleotides).

Regarding claim 6, Orum teaches the probe is a peptide nucleic acid (Figure 6, page 5335, where the PNA62 probe is a peptide nucleic acid).

Regarding claim 12, Orum teaches that:

- a) there is a first T_m for annealing of the extension primer to the first target sequence (Figure 6, where the primers anneal at 40°C)
- b) there is a second T_m for annealing of the probe to the second target sequence (Figure 6, where the probe anneals at 65°C)
- c) there is a third T_m for annealing of the probe to the mutant polynucleotides, wherein the second T_m is higher than the first T_m ($65^\circ\text{C} > 40^\circ\text{C}$) and wherein the first T_m is higher than the third T_m (page 5334, column 2 – page 5335 column 1 and Figure 5, where Orum states that when the second T_m is higher than the first T_m (61°C versus 52°C), amplification of both the wild-type and mutant sequences is inhibited (Figure 5, lane 2). Orum et al. further state that upon increasing the size of the mutant primer (and thereby increasing its T_m above the T_m of the probe this effect could be eliminated (Figure 5, lanes 8 and 10)).

Regarding claim 13, Orum teaches that the first target sequence and the second target sequence overlap (pages 5333-5334 teach the testing of overlapping first and second sequences and the results shown in Figure 6 were obtained using the “primer exclusion” configuration, where the sites overlap (page 5334, column 2).

Regarding claim 25, Orum teaches a method for selectively amplifying a mutant polynucleotide, in a mixture comprising mutant and wild-type polynucleotides, both the mutant polynucleotide and the wild-type polynucleotides having the same first target sequence, the wild-type polynucleotide having a second target sequence not present in the mutant polynucleotide, at least part of the second target sequence being located 3' of the first target sequence on the same polynucleotide strand of the wild-type polynucleotide, comprising:

- a) contacting the mixture with a probe complementary to the second target sequence to preferentially anneal the probe to the second target sequence of the wild-type polynucleotide rather than to a corresponding sequence in the mutant polynucleotide (Figure 6, page 3555, where the PNA62 probe meets these limitations)
- b) simultaneously with step (a) above, contacting the mixture with an extension primer complementary to the first target sequence in both the mutant and wild-type polynucleotides to anneal the primer to the first target sequence in both polynucleotides (page 3555, Figure 6, where the common reverse primer meets these limitations)
- c) contacting the mixture with a DNA polymerase and nucleoside triphosphates to extend the extension primers annealed to the polynucleotides by polynucleotide synthesis, the probe annealed to the wild-type polynucleotide limiting polynucleotide synthesis of the extension primer annealed to the wild-type polynucleotide, wherein the polynucleotide synthesis that uses the wild-type polynucleotide is blocked by the probe and the polynucleotide synthesis that uses the mutant polynucleotide is not blocked (page 3555, Figure 6).

Regarding claim 28, Orum teaches isolating the extension products from the mixture (page 3555, Figure 6, where the extension products are isolated by agarose gel electrophoresis).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the method of Afonina to the detection of mutant polynucleotides. Afonina taught that primer extension on a single-stranded template was specifically blocked by a complementary oligonucleotide conjugated to a minor groove binder annealed to the template downstream of the extension primer (pages 3201-3202 cited above). Afonina noted that only blocking oligonucleotides that were perfectly complementary to the template strand were capable of completely blocking primer extension (page 3201, column 2 – page 3202, column 1), thereby suggesting to an ordinary practitioner that the extension of a mutant polynucleotide would not be blocked by a probe perfectly complementary to a sequence found only in the wild-type polynucleotide. Afonina also stated, “The hybridization properties of ODN-CPDI3 conjugates warrant their further evaluation as diagnostic probes and as potential PCR clamping agents (page 3203, column 2).” Since Orum taught that PCR clamping was an robust and direct method of detecting mutations (see abstract), an ordinary practitioner would have been motivated to perform the method taught by Afonina using a mixture of mutant and wild-type polynucleotides in order to extend the applicability of the method to mutation detection. Since Afonina expressly suggested using the oligonucleotides in PCR clamping (i.e. blocking) reactions (page 3203, column 2), an ordinary practitioner would have been motivated to use the minor groove binder-conjugated oligonucleotides in either a PCR format as taught by Orum or the primer extension format taught by Afonina to detect mutant sequences in a mixture of wild-type and mutant polynucleotides. Finally, although neither Afonina nor Orum teach sequential addition of the primer and probe, MPEP 2144.04 IV.C notes, “Selection of any order of mixing ingredients is *prima facie* obvious.” Here, there is no particular reason why the order is shown to have any

effect on the reaction other than to add the probe first followed by the primer. Afonina even stated, "Inhibition of primer extension did not require a preannealing step (page 3202, column 2)." Therefore, in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is *prima facie* obvious as noted by the MPEP section above. The combined teachings of Afonina and Orum result in the instant claims 1-3, 6-9, 11-13, 25, and 28.

7. Claims 3, 4, 16, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Afonina et al. (PNAS (1996) 93: 3199-3204; newly cited) in view of either Rampersad et al. (US 5,830,712) or Sun et al. (Nature Biotechnology (February 2002) 19: 186-189) and further in view of Nollau et al. (Clinical Chemistry Laboratory Medicine (1999) 37: 877-881).

The combined teachings of Afonina and Rampersad **or** Afonina and Sun result in the method of claim 1, as discussed above.

None of the above references (Afonina, Rampersad, or Afonina) teach that the mutant and wild type polynucleotides are isolated from unrelated polynucleotides before or after the step of contacting the polynucleotides with the probe. These references also do not teach preferential isolation of the extension products.

Nollau teaches a method for enrichment of mutant alleles by chromatographic removal of wild type alleles. Single-stranded PCR products were loaded onto a chromatographic column containing streptavidin sepharose to which biotinylated oligonucleotides were bound that were complementary to the wild type sequence. The wild-type sequences bound to their immobilized complements and the flow-through contained an enriched population of mutant alleles. (See Methods section, and the first paragraph of Results, page 878).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use a sequence specific capture method as taught by Nollau in order to remove unrelated sequences prior to the amplification of mutant alleles using the methods resulting from the combined teachings of either Afonina and Rampersad **or** Afonina and Sun. Nollau taught that the chromatographic capture method described above produced a population highly enriched in mutant sequences (abstract: “enrichment of one mutant in up to 1,000 normal alleles has been achieved”). Where an initial purification step to remove unrelated sequences is desired prior to performing the method resulting from the combined teachings of either Afonina and Rampersad **or** Afonina and Sun, the teachings of Nollau would have provided strong motivation to employ the aforementioned sequence specific capture method. Two simple and well known modifications would have been required of the ordinary artisan: (1) addition of a biotin moiety to the common reverse primers of Rampersad or Sun and (2) immobilization of sequences complementary to wild type and mutant sequences in the column of Nollau.

Regarding claims 16 and 28, following enrichment by the method resulting from the combined teachings of either Afonina and Rampersad **or** Afonina and Sun, it would have been obvious to the person of ordinary skill, given the teachings of Nollau, to include a further purification/enrichment step comprising removal of any contaminating wild-type sequences using the aforementioned chromatographic separation method. Such a method, when performed as taught by Nollau, would have eliminated any residual wild type contaminants, thereby producing a further purified (preferentially isolated) enriched population of mutant sequences. Therefore, one of ordinary skill, interested in obtaining a highly purified, maximally enriched population of mutant polynucleotides, would have been motivated to incorporate the

chromatographic separation method of Nollau in the methods resulting from the combined teachings of either Afonina and Rampersad or Afonina and Sun to remove unrelated polynucleotides and/or preferentially isolate mutant sequences, thus resulting in the instantly claimed methods.

8. Claims 17-20, 23, 27, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dietmaier et al. (American Journal of Pathology (1999) 154(1): 83-95; newly cited) in view of Afonina et al. (PNAS (1996) 93: 3199-3204; newly cited) and further in view of Orum et al. (Nucleic Acids Research (1993) 21(23): 5332-5336).

Dietmaier teaches a method for multiplex analysis of microsatellite DNA comprising a primer extension preamplification (PEP) step followed by PCR amplification (see abstract).

Regarding claims 18, 19, 26, 29, and 30, the method of Dietmaier comprises the following steps (pp. 84-86):

- (a) obtaining a sample of biological material including microsatellite DNA (pages 84-85)
- (b) performing primer extension preamplification and isolating the extension products (page 85)
- (c) performing a single round (i.e. not nested) multicycle PCR amplification to amplify the primer extension products generated in step (b)
- (d) analyzing the extension products (page 85, column 2).

Regarding claim 20, Deitmaier teaches detection of BAT26 microsatellites (page 89, column 1).

Regarding claim 23, Deitmaier teaches simultaneous detection of two or more microsatellites (see abstract).

Regarding claim 27, Deitmaier teaches determining the size and abundance of the amplified extension products (see Figure 2, for example).

Dietmaier does not teach that the PEP reaction includes a blocking probe that prevents extension of contaminating wild-type polynucleotides.

The teachings of Afonina and Orum are discussed above.

The combined teachings of Afonina and Orum result in the method of claims 1-3, 6-9, 11-13, 25, and 28.

The above references do not teach application of the method to microsatellite DNA or PCR amplification of the primer extension products.

Regarding claim 17, Orum teaches a PCR amplification reaction using:

a) a first PCR primer that is complementary to a nucleotide sequence present in the 3' end of a long extension product, but not present in a short extension product (Figure 6, page 5335, where the allele-specific primer for the mutant sequences is complementary to a sequence present at the 3' end of a long extension product (the amplified mutant sequence), and is not present in a short (wild type) extension product)

b) a second PCR primer that is identical to a nucleotide sequence present in both the long and short extension products (Figure 6, page 5335, where the common reverse primer is identical to a sequence present in both wild type and mutant products).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use the method of mutation detection resulting from the combined teachings of Afonina and Orum to improve the sensitivity of the microsatellite mutation assay taught by Dietmaier. Afonina expressly taught that primer extension on a single-strand template was specifically arrested upon annealing of a perfectly complementary oligonucleotide conjugated to a minor groove binder to the template (see above). Likewise, Orum taught that PNA clamping greatly improved the sensitivity and specificity of PCR methods designed to detect mutant polynucleotides. Since Dietmaier specifically commented about the need to eliminate contaminating wild-type polynucleotide sequences (page 83, column 2), an ordinary practitioner would have been highly motivated to seek a simple, efficient, and specific means of eliminating such sequences, thereby improving the accuracy of the method. Inclusion of a blocking probe, as taught by Afonina, in the I-PEP reaction would have provided a simple, efficient and highly specific solution to this problem, and therefore, an ordinary practitioner would have been motivated to include such a probe in the I-PEP reaction. Finally, although Afonina does not teach sequential addition of the primer and probe, MPEP 2144.04 IV.C notes, “Selection of any order of mixing ingredients is *prima facie* obvious.” Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the probe first followed by the primer. Afonina even stated, “Inhibition of primer extension did not require a preannealing step (page 3202, column 2).” Therefore, in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is *prima facie* obvious as noted by the MPEP section above. The combined teachings of Dietmaier, Afonina, and Orum result in the instant claims 17-20, 23, 25-27, 29, and 30.

9. Claims 21, 22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dietmaier et al. (*American Journal of Pathology* (1999) 154(1): 83-95; newly cited) in view of Afonina et al. (*PNAS* (1996) 93: 3199-3204; newly cited) and further in view of Orum et al. (*Nucleic Acids Research* (1993) 21(23): 5332-5336) and further in view of Percesepe et al. (*Genes Chromosomes Cancer* (2000) 27: 424-429) and Suraweera et al. (*Gastroenterology* (December 2002) 123: 1804-1811).

The combined teachings of Dietmaier, Afonina, and Orum result in the method of claim 19, as discussed above.

None of the above references teach the detection of the NR-21 microsatellite or the simultaneous detection of the BAT-26 and TGF-B RII microsatellites.

Regarding claim 21, Suraweera teaches that NR-21 microsatellites are associated with colon cancer (page 1809, column 1, last paragraph).

Regarding claim 24, Percesepe teaches that BAT-26 and TGF- B RII microsatellites are associated with colon cancer (abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to detect mutations in the NR-21 microsatellites and/or simultaneously detect mutations in the TGF- B RII and BAT-26 microsatellites when performing the method resulting from the combined teachings of Dietmaier, Afonina, and Orum. The method of Dietmaier is directed in some embodiments to the detection of microsatellite mutations indicative of colon cancer (page 85, column 1). Percesepe and Suraweera taught that mutations in the NR-21, BAT-26 and TGF- B RII microsatellites were useful colon cancer markers (abstract of Percesepe and page 1809, column 1 of Suraweera). These teachings of Percesepe and Suraweera would have

motivated the ordinary practitioner of the method resulting from the combined teachings of Dietmaier, Afonina, and Orum to include these microsatellites in order to provide additional positive indicators of cancer and improve the accuracy of the resulting diagnosis.

Response to Arguments

10. **Objections to the Specification**

Applicant's arguments, see page 10, filed September 1, 2006, with respect to the objections to the specification have been fully considered and are persuasive. The objection to the specification has been withdrawn.

Claim Objections

Applicant's arguments, see page 10, filed September 1, 2006, with respect to the objection to claims 1-27, have been fully considered and are persuasive. Applicant's amendment to claim 1 overcomes the objection, and therefore, it has been withdrawn.

Rejections under 35 U.S.C. 112, 2nd paragraph

Applicant's arguments, see page 10, filed September 1, 2006, with respect to the rejection of claims 25-27, have been fully considered and are persuasive. Applicant's amendment to claim 25 overcomes the rejection, and therefore, it has been withdrawn.

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Rejections under 35 U.S.C. 102

Applicant's arguments, see pages 10-12, filed September 1, 2006, with respect to: (a) the rejection of claims 1, 2, 5, 6, 14, 15, 18, 25, and 27 as anticipated by Sun, (b) the rejection of claims 1, 2, 7-12, 14, 18, 25, and 27 as anticipated by Rampersad, (c) the rejection of claims 1-3, 6, 12-14, 17, 18, 25 and 27 as anticipated by Orum, and (d) the rejection of claims 1, 2, 7, 9, 11, 14, 18, and 25-27 as anticipated by Seyama have been fully considered and are persuasive.

These references do not teach the new limitation that only one strand of a double-stranded target nucleic acid is capable of polymerase-mediated extension. Therefore, the rejections under 102 have been withdrawn.

Rejections under 35 U.S.C. 103

Applicant's arguments with respect to claims 3, 4, 16, and 19-24 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
November 8, 2006

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
11/9/06